Linking high-throughput data to human exposures

By Catherine Sprankle

NIEHS scientists and colleagues throughout the world are evaluating the use of high-throughput methods to identify chemicals that could cause human illness. Once such chemicals are identified, a process known as *in vitro* to *in vivo* extrapolation links the high-throughput data to human doses. The process takes into account metabolic differences between cell-based systems and whole organisms.

In a Jan. 27 webinar *(http://ntp.niehs.nih.gov/pubhealth/evalatm/3rs-meetings/past-meetings/commprac-2015/index.html)*, organized by the NTP Interagency Center for the Evaluation of Alternative Methods *(http://ntp.niehs.nih.gov/pubhealth/evalatm/index.html)* (NICEATM; see sidebar), more than 250 viewers from around the world learned about *in vitro* to *in vivo* extrapolation from two experts.

Wambaugh used mathematical models and computer simulations to predict doses that would result from chemical exposure in humans. (Photo courtesy of Keith Tarpley)

The webinar featured presentations by John Wambaugh, Ph.D., physical scientist in the National Center for Computational Toxicology at the U.S. Environmental Protection Agency (EPA), and Barbara Wetmore, Ph.D., senior research investigator at the Hamner Institutes for Health Sciences. Organized on behalf of the Interagency Coordinating Committee on the Validation of Alternative Methods *(http://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/index.html)* (ICCVAM), it was the first in a series of Communities of Practice webinars that will provide in-depth examinations of topics related to chemical screening and safety testing.

Building on ToxCast data

EPA scientist Anna Lowit, Ph.D., co-chair of ICCVAM, introduced the speakers. “This is a very exciting time in risk assessment and toxicology,” she said. Lowit emphasized the key role that *in vitro* to *in vivo* extrapolation plays in applying high-throughput screening data to human risk assessment.

Wetmore described experiments that measured the effects of specific metabolic enzymes on a group of chemicals. (Photo courtesy of The Hamner Institutes for Health Sciences)

Wambaugh described both the lab work and the computations required to link high-throughput screening data to human doses of concern. According to Wambaugh, two factors complicate the process of making that link — diversity in human sensitivity and variations in chemical properties that result in some chemicals being retained by the body longer than others. Wambaugh described ongoing studies by EPA and collaborators to generate human metabolism data. “These data will eventually allow determination of human oral equivalent doses for most ToxCast *(http://www.epa.gov/ncct/toxcast/)* chemicals,” he said.

ToxCast is a multiyear effort launched by EPA in 2007 that uses high-throughput screening to expose living cells or isolated proteins to chemicals. The cells or proteins are then screened for changes in biological activity that may suggest potential toxic effects.

Examining the effects of human diversity

Wetmore discussed the effects of human diversity. “Relying on data for a generic population could lead us to seriously underestimate the risk to a susceptible subpopulation,” she said. Wetmore described *in vitro* to *in vivo* extrapolation studies that accounted for human variation and produced predictions of how the body’s handling of chemicals might differ in healthy people compared to ill people, adults compared to children, and in people with different genetic backgrounds.

These studies predicted populations that might be most susceptible to toxicity from a particular chemical. For example, when comparing populations with similar external exposures to the insecticide carbaryl, newborns were predicted to have higher blood levels

Finding alternatives to animal testing

The term alternative methods refers to methods of research and testing that use fewer or no animals, or that reduce animal pain and distress. Congress established several groups to ensure the involvement of all

of the substance than other populations. For the fungicide difenoconozole, people with kidney disease were predicted to have higher blood levels.

Several webinar viewers asked questions of each of the speakers. In his closing remarks, NICEATM Director Warren Casey, Ph.D., noted the strong interest in the webinar and shared that NICEATM would explore organizing a workshop on this topic.

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stakeholders in development of such methods.

- The Interagency Coordinating Committee on the Validation of Alternative Methods *(http://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/index.html)* (ICCVAM) coordinates the activities of member federal agencies to replace, reduce, or refine animal use.
- The NTP Interagency Center for the Evaluation of Alternative Methods *(http://ntp.niehs.nih.gov/pubhealth/evalatm/index.html)* (NICEATM) is an office within the National Toxicology Program (NTP) that supports ICCVAM activities and NTP projects. The center is involved with development of novel approaches to testing.

NICEATM supports international efforts to develop new test methods

NICEATM scientists joined international collaborators at meetings in Kyoto, Japan, to assess the progress of other efforts to develop nonanimal methods for chemical safety testing.

- Nicole Kleinstreuer, Ph.D., a NICEATM support contractor, participated in meetings Jan 29-31 of the validation study management team. The validation studies are designed to determine the usefulness and limitations of methods that use collagen membranes to identify potential eye irritants and skin sensitizers. Experimental work on the eye irritation study is complete and the method will be submitted for international approval later this year. Experimental work on the skin sensitization study will be completed later this spring.
- Casey participated in two study management team meetings in mid-February to review results from ongoing validation studies of new test methods. One method uses cultured corneal cells to identify eye irritants. The other uses embryonic stem cells to identify potential developmental toxicants.

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